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CDER's emerging technology team

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Biotechnology Manufacture and CDER's ETT

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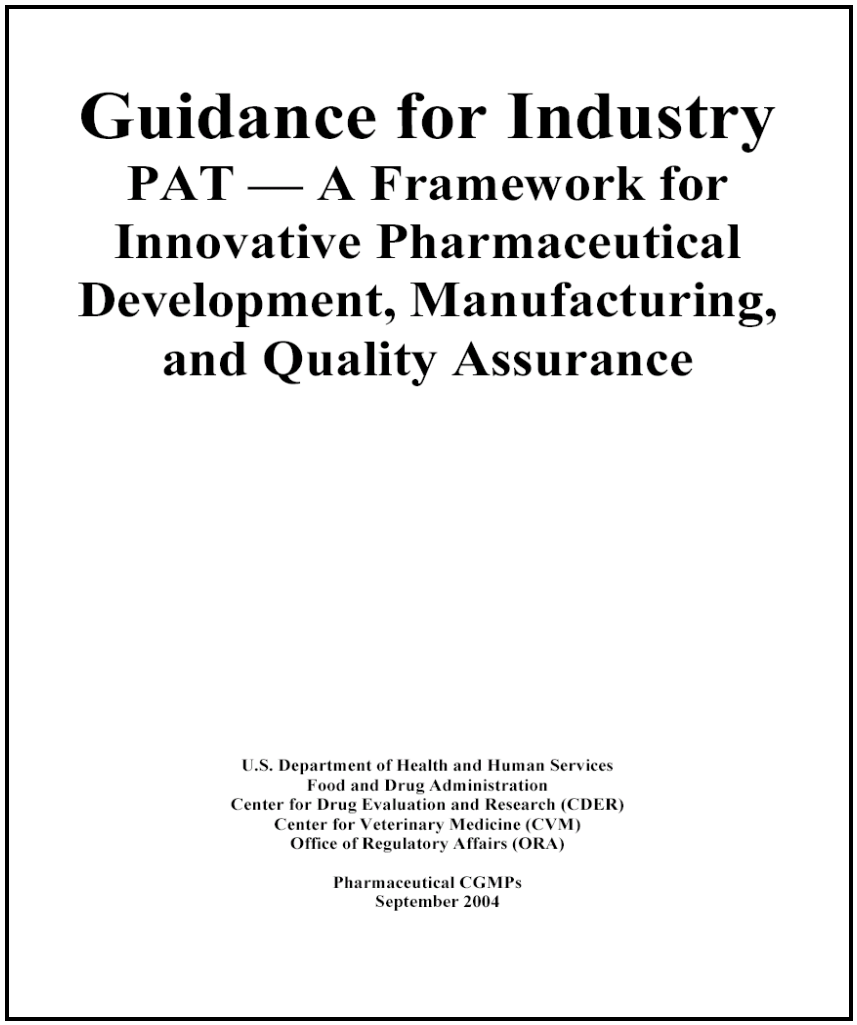
Views presented are those of the speaker & not necessarily official FDA policy

Process Analytical Technology (PAT)

PAT Guidance



- Released September 29, 2004
- Scientific principles and tools
  - Process Understanding
  - PAT Tools
  - Risk-Based Approach
  - Integrated Approach
- Regulatory Strategy accommodating *innovation*
  - Training
  - Lab research
- www.fda.gov/cder/gmp
- Can this be applied to biotech?

The Essence of PAT

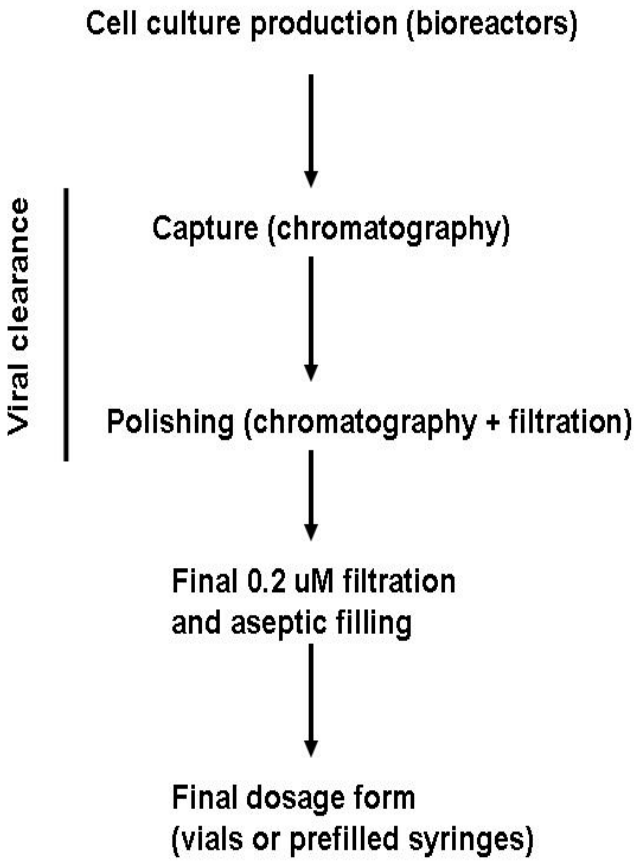
Product quality is monitored and controlled during the manufacturing process.

Process decisions are based on assessments of material attributes.

- Forward-feed of incoming material

- Critical product attributes measured/assessed either
  - Instantaneously (on-line, in-line, at-line) or
  - Before decision point (near at-line)

Major Stages in Bioprocessing



Each stage has one or more unit operations (e.g. bioreactors, columns, etc.)

In biotech, PAT can be applied on a unit operation basis

Biotech Unit Operations are composed of sequential steps

Cell culture

- Bioreactor prep
- Media fill
- Inoculate
- Feed
- Harvest

CHROMATOGRAPHY

- Equilibrate the column
- Load the column
- Wash away unbound material
- Elute the bound material

Transition from one step to the next

Decision points

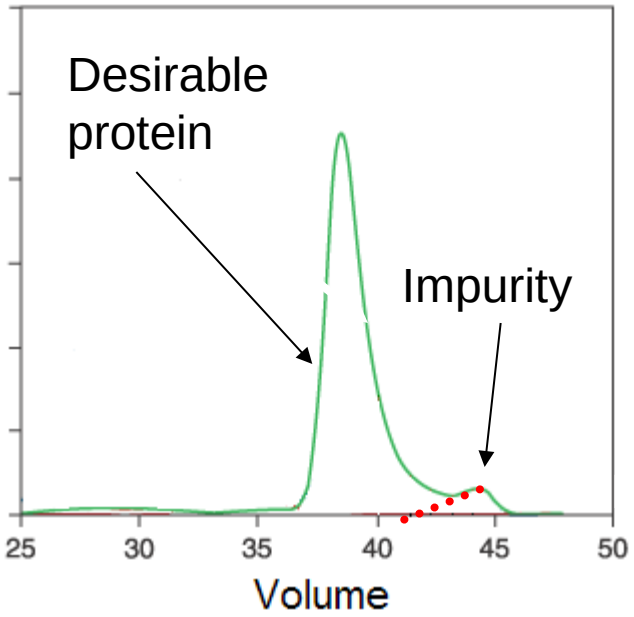
- Points in a process at which transition decisions are made.

Decision criteria

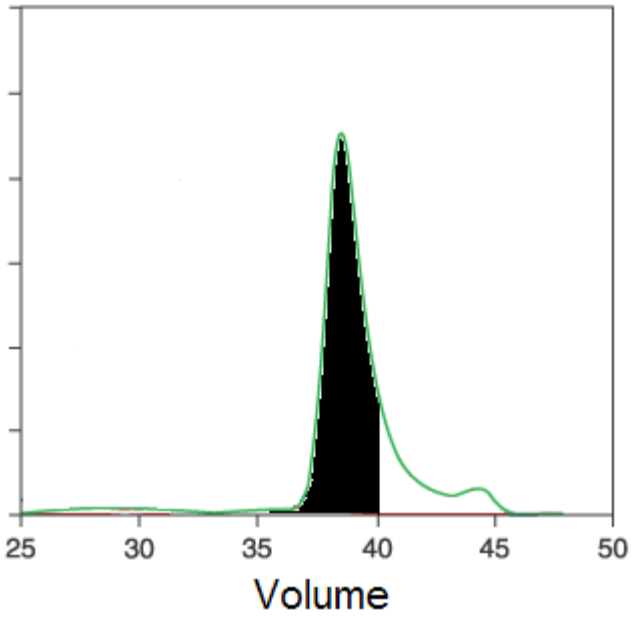
- The information that triggers a transition.

- **Note:** In PAT
  - *Decision point and criteria must be close enough in timing for process control.*
  - *Criteria related to product attribute*

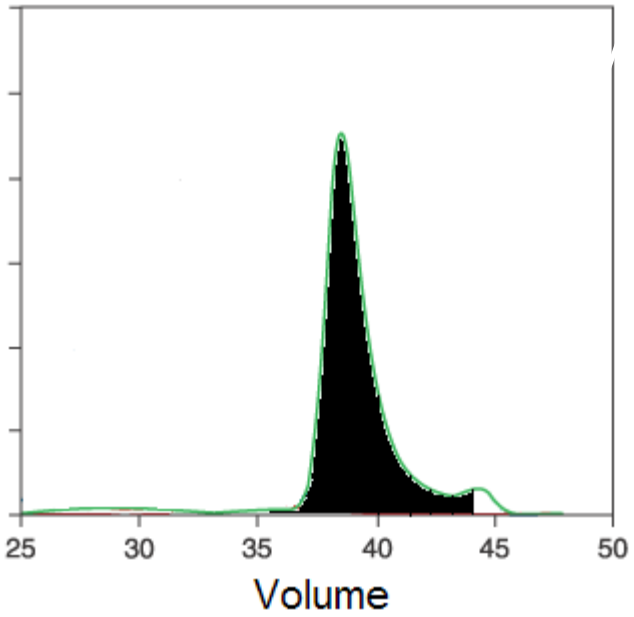
Decision Criteria Example: eluting a protein from a column



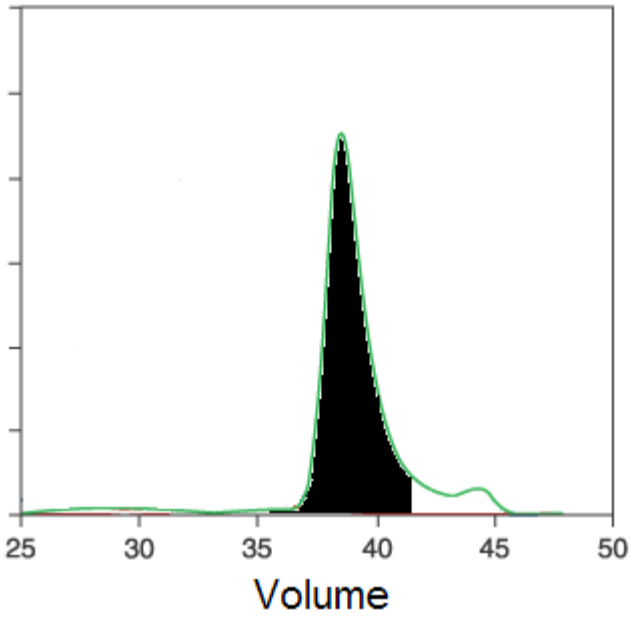
Decision Criteria – 40 LITER CUT: Yield loss



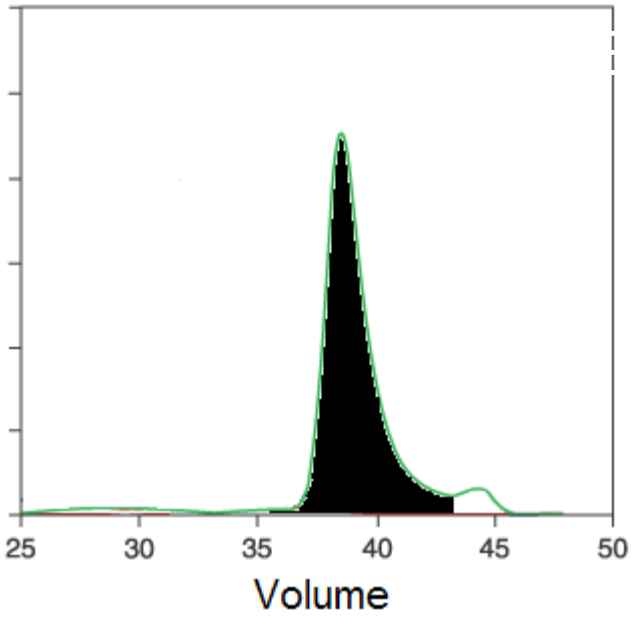
Decision Criteria – 2 Col. Vol. Cut: Impurities



Decision Criteria – A280 Target Cut: Better, but still yield loss

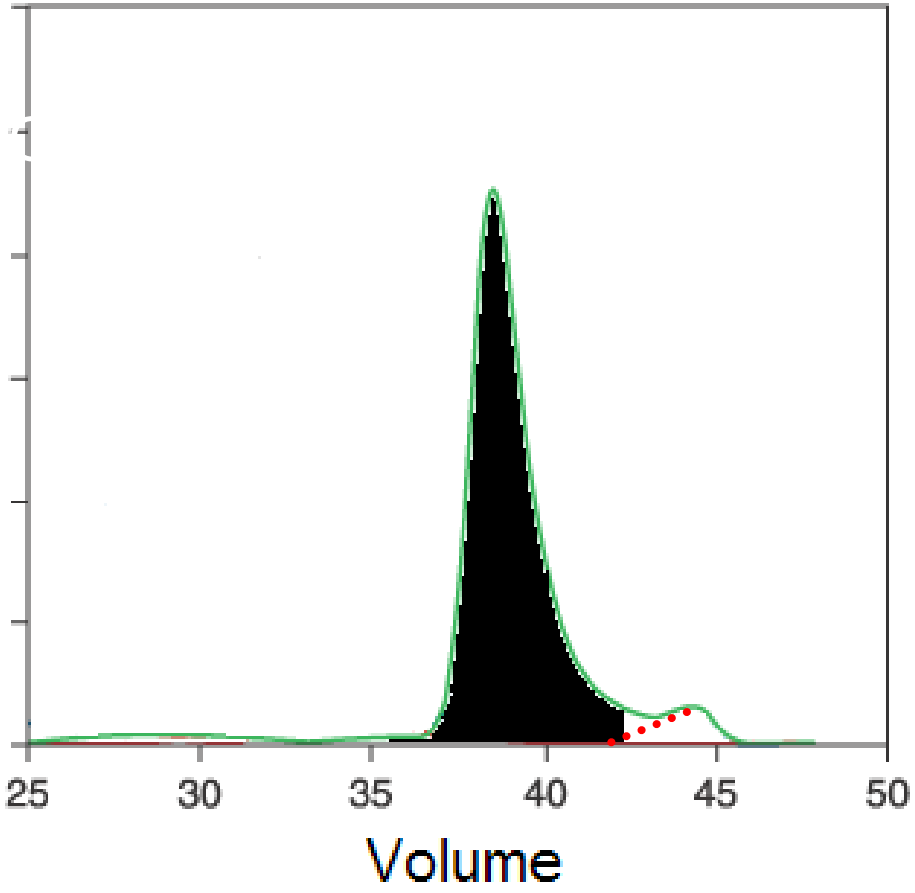


Decision Criteria – A280 Slope Cut: Better, but still has impurities



Decision Criteria – Component Cut:

Best balance *if* impurity can be monitored in-line (or near-at-line) to allow active control



Aggregates in theory can be measured/detected via in-line capable methods like CD, light scattering, FTIR, A_{410}, other techniques

(Brorson and Phillips, BioProcess Intl Nov. 2005)

The biotech world presents a unique set of challenges:

- Production by finicky and highly complex cell-based biological systems
  - highly sensitive to external conditions;
- In-process intermediates can be complex mixtures
  - desired protein may be a fraction of the bulk liquid;
- Worrisome, low level impurities (e.g., viruses) still a concern
  - even when present at levels undetectable by even the most sensitive in-line/on-line/at-line technologies.
  - Removal validation for now

- In contrast, some significant challenges for small molecule drugs may not apply to biotech;
  - blending of aqueous protein solutions

New approaches enabling PAT

- Systems Biology
  - Metabolomics, proteomics, etc. may identify relationships between measurable process variables and cell culture state
- Multivariate data analysis (MVDA)
  - Biotech processes generate huge datasets amenable to MVDA to predict process outcomes

New approaches enabling PAT- 2

- Robotics and automation
  - Will enable efficient and consistent sampling of complex process fluids
- Advances in Mass spectroscopy
  - Rapid comprehensive biochemical analysis
- Capacitance probes to measure culture mass
  - On-line measurement of cell biomass and viability

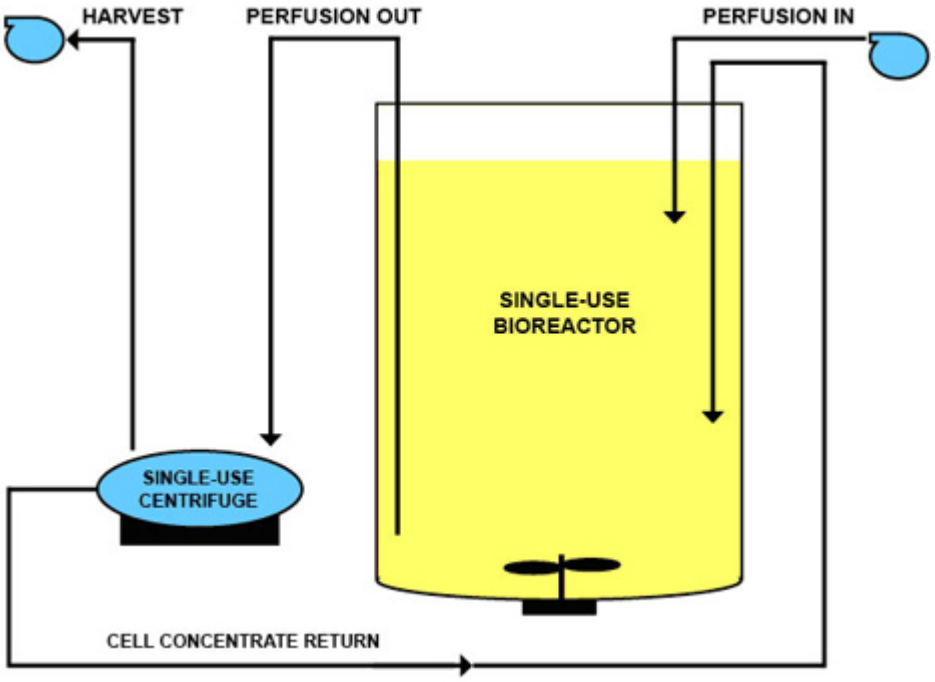
Continuous Processing

Continuous mode processing in Biotech

- Most unit operations are batch mode
  - Discrete input → unit op → discrete output
- Examples:
  - Batch or fed-batch mode bioreactor
  - Most B&E and flow through columns
- Continuous mode processing steps do exist
  - Usually one unit within a train of batch mode

Continuous-mode Bioreactor

- Media is perfused in and out
  - Rate determined by culture activity
- Excess cells collected by spin basket or other means
- Used in licensed biotech products for seed-train expansion and production phase



Opportunity for continuous processing: Simulated Bed Chromatography

- Two or more columns, connected to one another in series
- Mobile-phase pump, via a six-port, two-position valve.
- Switching of the valve will "leapfrog" the columns over one another.
  - Effluent can be collected (product) or sent on to next column (if feedstock partially depleted on product)
- Used extensively in chemical and food industry
  - In theory can be applied to bioprocessing but not implemented on wide scale

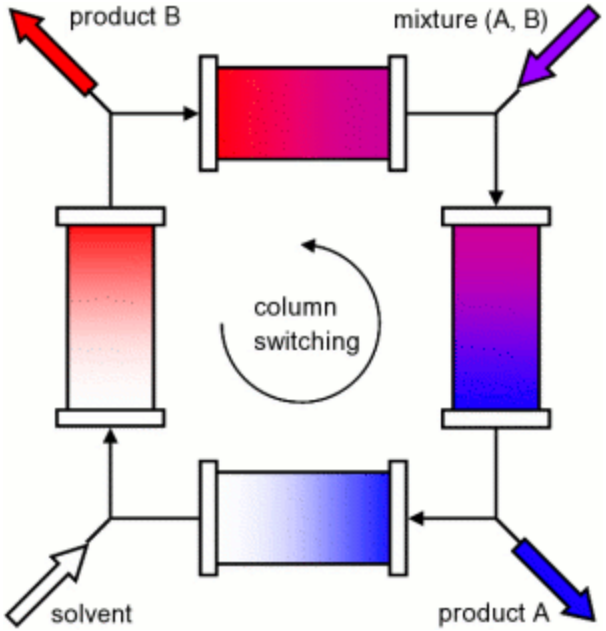


Image from
www.worldofchemicals.com

Regulatory issues…

- Continuous chromatography (SMB)
  - Is the separation power equivalent (i.e. higher impurities in eluate, yield loss)
  - How do you validate viral clearance?
    - In-line spiking & grab samples?
  - How do you design a representative scale down model?
- Continuous bioreactors mode
  - Longer time for genetic or production drift of culture
  - More time and portals for system breach- bacterial contamination
  - Viral safety- longer period for introduction & growth of virus

CDER's Emerging Technology Team

What is the Emerging Technology Team (ETT)?

- A small cross functional team with representation from all relevant CDER review and inspection programs
- Vision: Encourage and support the adoption of innovative technology to modernize pharmaceutical development and manufacturing where the Agency has limited review or inspection experience. Includes:
  - Innovative or novel product, manufacturing process, or analytical technology subject to CMC review
  - Existing or planned submission(s)

The ETT Charter

- Provides a forum for knowledge sharing and scientific discussion
- Provides consistency, continuity and predictability
  - Facilitates establishment of review and inspection standards and policy
- Supports GMP manufacture of quality product over the lifecycle
- Long term goals:
  - Engage international regulatory agencies to share learnings and approaches
  - Modernizing pharmaceutical development and manufacturing

Role of ETT

- Provides perspective on quality review and inspections
  - ETT members serve to lead/co-lead cross-functional team during review process
  - Participates or supports relevant inspection(s) and/or pre-operational visits
  - Identify and capture decisions that may inform future FDA approaches and decisions
- Serve as advocates for innovative technology while balancing risk vs. benefit
- Identify and evaluate roadblocks relating to existing guidance, policy, or practice
- Early applicant engagement with the ETT is recommended
- Contact us: **CDER-ETT@fda.hhs.gov**

Thank You

Are there questions?